REMARKS

Claims 38, 39, 44-51, 53, 73-76, and 81-83 are pending in the application and have been examined. Claims 38, 39, 44-51, 53, 73-76, and 81-83 stand rejected. Claims 38 and 73 have been amended. New Claims 84-87 have been added. No new matter has been introduced. Reconsideration and allowance of Claims 38, 39, 44-51, 53, 73-76, and 81-87 is respectfully requested.

The Rejection of Claims 38, 39, 44-51, 53, 73-76, and 81-83 Under 35 U.S.C. §103(a) as Being Unpatentable Over U.S. Patent No. 6,413,511 (Glorioso et al.)

Claims 38, 39, 44-51, 53, 73-76, and 81-83 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,413,511 (Glorioso et al.).

The Examiner characterizes Glorioso et al. as disclosing a method of regenerating joint cartilage by intra-articular injection of a composition comprising compounds that both promote chondrocyte anabolism and inhibit chondrocyte catabolism (Col. 6, lines 3-10). As noted by the Examiner, the method of treating cartilage defects disclosed by Glorioso et al. includes injecting synovial cells and chondrocyte cells genetically modified to express interleukins and transforming growth factors, such as beta 1, 2, or 3, where the delivery is made intra-articularly into the joint space and alleviates the defect (Col. 14, lines 28-44; Col. 20, lines 10-33) (emphasis added). The Examiner asserts that these genetically modified cells are agents that directly promote anabolic activities. The Examiner admits that Glorioso does not specifically teach a formulation comprising the combination of compounds recited in the claims, however the Examiner has taken the position that the reference indicates that the formulation intends to both promote anabolic activity while inhibiting cartilage catabolism, with reference to Col. 28, lines 10-20. The Examiner concludes that it would have been obvious to include a DNA

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fragment that promotes anabolic activity and another DNA fragment that inhibits catabolic activity in order to be more effective in treating defects. Applicants respectfully traverse this ground of rejection for the following reasons.

As an initial matter, while not acquiescing to the Examiner's position, but in order to clarify the invention, independent Claims 38 and 73 have been amended to recite, in relevant part:

> delivering to the joint a composition in solution comprising a therapeutically effective amount of a first chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent, wherein the first chondroprotective agent is an anabolic chondroprotective drug that directly promotes cartilage anabolic processes and the second chondroprotective agent is an inhibitor of cartilage catabolism, and the solution is delivered locally to the joint . . . .

Support for this amendment is found in the specification (published as WO 01/07067); for example, at page 8, lines 26-36; page 10, lines 15-19; page 15, lines 25-36; page 16, lines 26-30; and page 34, line 32, to page 36, line 17.

Glorioso et al. Fails to Render the Claimed Invention Unpatentable

Glorioso et al. fails to render the claimed invention unpatentable. *KSR* confirmed that the Grahm Factor Analysis should be used in determining whether a claimed invention is obvious under Section 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007). This analysis includes assessing the rejected claims, the scope and content of the cited art, and the differences between the rejected claims and the cited art. *Id.* at 1734. As will be shown, a *prima facie* case of obviousness has not been established because (1) Glorioso et al. fails to teach every limitation of the claimed invention, and (2) there is no motivation or expectation of success to modify

Glorioso et al. as proposed by the Examiner to arrive at the claimed invention because Glorioso et al. teaches directly away from the claimed invention.

1. The differences between the rejected claims, as amended, and the cited art

Glorioso et al. is generally directed to methods of introducing at least one DNA sequence expressing a protein or protein fragment which substantially alleviates articular cartilage defects into cells and transplanting these genetically modified cells into a joint.

As stated in Glorioso et al.:

> The present invention discloses ex vivo and in vitro techniques for delivery of a DNA sequence of interest to the connective tissue cells of the mammalian host. The ex vivo technique involves prior removal and culture of target autologous connective tissue cells, in vitro infection of the DNA sequence, DNA vector or other delivery vehicle of interest into the connective tissue cells, followed by transplantation to the modified connective tissue cells to the target joint of the mammalian host, so as to effect in vivo expression of the gene product of interest. [Col. 1, lines 35-45 (emphasis added).]

In sharp contrast to the gene therapy methods and transplantation of genetically modified cells into joints as described in Glorioso et al., the methods of the present invention, as amended, are directed to delivering to a joint a composition in solution comprising a therapeutically effective amount of a first chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent, wherein the first chondroprotective agent is an anabolic chondroprotective drug that directly promotes cartilage anabolic processes, wherein the anabolic chondroprotective agent is selected from the group consisting of members of the transforming growth factor-β superfamily, including TGF-β agonists and bone morphogenic protein agonists

that promote cartilage anabolic processes, and insulin-like growth factors that promote cartilage anabolic processes.

As described in the specification, the local delivery of the drug combination of the present invention achieves "an instantaneous therapeutic concentration of chondroprotective agents within the joint." Page 36, lines 7-9. As further stated in the specification, an advantage of the present invention is that "direct, local delivery to the joint enables use of novel, pharmaceutically active peptides and proteins, including cytokines and growth factors, which may not be therapeutically useful if limited to systemic routes of administration." Specification at page 36, lines 14-17.

As further described in the instant specification, exemplary anabolic chondroprotective agents that directly promote cartilage anabolic processes are selected from the group consisting of members of the transforming growth factor-β superfamily, including TGF-β agonists and bone morphogenic protein agonists that promote cartilage anabolic processes, and insulin-like growth factors that promote cartilage anabolic processes, including proteins or peptides.

For example, as stated in the specification, "Transforming growth factor-beta (TGF-beta) subfamily members are 25 kD pleiotropic, multifunctional proteins . . . ." Page 47, lines 25-26. As further stated in the specification, "Bone morphogenetic proteins (BMPs) are multifunctional regulators of cell growth, differentiation, and apoptosis that belong to the transforming growth factor (TGF-beta) superfamily." Page 48, lines 12-14.

As further stated in the specification:

> Naturally occurring TGF-beta and BMP agonists as well as synthetic or human recombinant (rh) agonists suitable for use in the cartilage-protective solution of the present invention may interact with any of the BMP receptors described above. As used herein, the term 'TGF-

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beta and BMP agonists' includes fragments, deletions, additions, amino acid substitutions, mutations and modifications thereof which retain the biological characteristics of the naturally occurring human TGF-beta and BMP agonist ligands. [Specification at page 49, lines 4-10.]

As further described in the specification:

> Within the context of defining TGF-beta and BMP agonists as pharmacological agonists, the term TGF-beta and BMP agonists includes, but is not limited to: (1) peptide sequences which correspond to naturally (endogenous) produced amino acid sequences or fragments thereof, (2) recombinant TGF-betas and BMPs which are truncated or partial sequences of the full length naturally occurring TGF-beta and BMP amino acids which retain the ability to bind cognate their respective receptor and retain biological activity and analogs thereof, and (3) chimeric TGF-betas and BMPs which are recombinant polypeptides comprised of truncated or partial sequences corresponding to a portion of the full length amino acid sequences attached through oligomers (e.g., amino acids) to a sequence corresponding to a portion of an IgG polypeptide (e.g., IgG hinge and Fc domain) which retain the ability to bind the cognate receptor and retain biological activity. [Specification at page 51, lines 10-21.]

Therefore, it is demonstrated that Glorioso et al. does not teach or suggest a method of inhibiting cartilage degradation comprising delivering to the joint a composition comprising an anabolic chondroprotective drug that directly promotes cartilage anabolic processes in combination with an inhibitor of cartilage catabolism, as claimed.

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2. The differences between the rejected claims and the cited art are not obvious differences

There is no apparent reason to modify the methods of Glorioso et al. as proposed by the Examiner to replace the genetically modified cells with an anabolic chondroprotective drug that directly promotes cartilage anabolic processes (e.g., proteins, peptides, or chemical compounds). As stated in M.P.E.P. § 2143.01, "Rejections on obviousness cannot be sustained by mere conclusory statements, instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusions of obviousness." M.P.E.P. § 2143.01, citing *KSR*, 127 S.Ct at 1741, quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). In the context of an obviousness rejection, the Supreme Court explained the importance of "identify[ing] a reason" why a skilled artisan would be prompted to arrive at the presently claimed invention. *KSR*, 127 S.Ct. at 1741.

As noted above, Glorioso et al. discloses an approach that relies on transfection of a DNA sequence into cells, which are then transplanted into the joint of a subject, thus effecting expression of the gene product of interest in the joint. Glorioso et al. does not teach or suggest intra-articular administration of a composition comprising an anabolic chondroprotective drug that directly promotes cartilage anabolic process. Rather, Glorioso et al. teaches directly away from the claimed invention by describing the disadvantages of an approach involving intra-articular administration of drugs that directly promote cartilage anabolic processes. For example, Glorioso et al. states,"[K]nown intra-articular injection of joints provides direct access to a joint. However, most of the injected drugs have a short intra-articular half life. The present invention solves these problems by introducing into the connective tissue of a mammalian host genes encoding for proteins that may be used to treat the mammalian host." Col. 18, lines 59-64.

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Glorioso et al. further states:

> Thus, the access of large drug molecules, for example, proteins, to the joint space is substantially restricted. Intra-articular injection of drugs circumvents those limitations; however, the half-life of drugs administered intra-articularly is generally short. Another disadvantage of intra-articular injection of drugs is that frequent repeated injections are necessary to obtain acceptable drug levels at the joint spaces for treating a chronic condition such as, for example, arthritis. [Col. 3, lines 40-49.]

Glorioso et al. further teaches away from the claimed invention with the following statement:

> [T]he only other way of delivering potentially arthriotogenic compounds to the joint is by intra-articular injection. Not only are such compounds quickly cleared from joints, but the effects of bolus injections of these compounds do not accurately mimic physiological conditions where they are constantly produced over a long period of time. In contrast, the gene transfer technologies of this invention permit selected proteins of known or suspected involvement in the arthritic process to be expressed intra-articularly over an extended period of time, such as for example, at least a three month period. [Col. 32, lines 29-39.]

It is further noted that Glorioso et al. explicitly distinguishes the teachings of numerous patents that disclose the administration of drugs such as chemical compounds and proteins from the method of introducing genetically modified cells into joints (see Col. 4, line 1, to Col. 5, line 58). Glorioso concludes, "The various techniques disclosed to date to treat full thickness cartilage defects have had variable and limited success." Col. 5, lines 59-61.

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Therefore, it is demonstrated that Glorioso et al. does not teach or suggest the present invention. Moreover, Glorioso provides no motivation or expectation of success to arrive at the claimed invention because it teaches directly away from the present invention. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that was taken by the applicant. *Tec Air Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999)). That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness. See *Winner Int'l Royalty Corp. v. Wang*. 202 F.3d 1340, 1349-50 (Fed. Cir. 2000)).

3. Evidence of unexpected results demonstrates the patentability of the rejected claims

As stated in M.P.E.P. § 2142, "If the Examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." However, despite the absence of a *prima facie* case of obviousness, in order to facilitate prosecution, applicants previously submitted an extensive collection of data during prosecution of the present application, summarized in applicants' response dated March 23, 2009, demonstrating the unexpected results of the present invention including (1) non-prior art references (publications by Studer et al.) that were submitted with the response filed by applicants on January 3, 2006; and (2) additional experimental data that was submitted with the response filed by applicants on November 6, 2006. The experimental data previously provided by applicants is commensurate in scope with the pending claims, as amended, and demonstrates the surprising and remarkable effect that the evaluated inhibitors of cartilage catabolism, when administered together with an anabolic chondroprotective agent that directly promotes cartilage anabolic processes, have the potential to not only inhibit inflammation and matrix degradation, but to also restore the ability of the diseased chondrocytes to respond to the evaluated anabolic growth factors.

Thus, without the benefit of the applicants' disclosure, one of skill in the art would not be motivated by the teachings of the cited references, or by general knowledge in the art, to arrive at the claimed invention, and would have no reasonable expectation of success in practicing the invention as claimed. Accordingly, because the cited references teach directly away from the claimed invention, and because the general knowledge of one skilled in the art would not provide any basis or motivation to arrive at the claimed invention, Claims 38, 39, 44-51, 53, 73-76, and 81-83 are believed to be clearly patentable under 35 U.S.C. § 103(a) over U.S. Patent No. 6,413,511 (Glorioso et al.). Removal of this ground of rejection is respectfully requested.

New Claims

New Claims 84-87 have been added. No new matter has been introduced.

Claims 84 and 86 depend from independent Claims 38 and 73, respectively, and further recite "wherein the anabolic chondroprotective drug that directly promotes cartilage anabolic processes is a protein or peptide." Support is found throughout the specification as filed; for example, at page 9, lines 20-28; page 47, lines 25-27; page 51, lines 10-21; and page 82, line 1, to page 89, line 36.

Claims 85 and 87 depend from independent Claims 38 and 73, respectively, and further recite "wherein the anabolic chondroprotective drug that directly promotes cartilage anabolic processes is a chemical compound." Support is found throughout the specification as filed; for example, at page 6, line 30, to page 7, line 21; page 9, lines 22-23; and page 82, line 1, to page 89, line 36.

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Conclusion

In view of the foregoing remarks, applicants respectfully submit that all of the pending claims are in condition for allowance. Reconsideration and favorable action is requested. The Examiner is further requested to contact the applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

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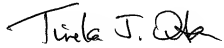

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